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Case report

Peripheral neuropathy arose in the trigeminal nerve during chemotherapy with docetaxel: A report of two cases

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ABSTRACT

Peripheral neuropathy is the major adverse event during administration of the taxanes, including paclitaxel and docetaxel. Among oral adverse events, oral mucositis is relatively common, but the occurrence of trigeminal nerve disorders is rare. Two cases of trigeminal nerve disorders, one involving the inferior alveolar nerve, the buccal nerve and the lingual nerve and the other the lingual nerve, caused by docetaxel are presented.

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1. Introduction

The taxanes, including paclitaxel and docetaxel, have been used in the treatment of breast, prostate, lung, pancreatic, gynecological, head and neck, and other solid tumors [1]. The antineoplastic mechanism of taxanes is inhibition disassembly of tubulin from the microtubule polymer, but paclitaxel and docetaxel have slight differences in their molecular pharmacology, pharmacokinetics, and pharmacodynamics that result in distinct clinical effects [1]. Chemotherapeutic agents can treat malignant tumors effectively, but at the same time, they can produce adverse events that may, when severe, require dose reduction or discontinuation of the chemotherapy [1]. Peripheral neuropathy is the major adverse event during administration of taxanes, with sensory symptoms that include tingling, numbness, and spontaneous and cold-induced burning pain [2]. Peripheral neuropathy occurs predominantly in anatomical structures innervated by the longest nerves in a symmetrical manner, mainly in the distal hands and

feet [3], but there are occasional cases of peripheral neuropathy involving the face [3,4]. Taxane-induced peripheral neuropathy is found in as many as 90% of treated patients, but it is less frequent with docetaxel than with paclitaxel [5].

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Adverse events in the oral cavity described in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.0) include nervous system disorders such as dysgeusia, facial nerve disorder, and trigeminal nerve disorder, as well as gastrointestinal disorders such as oral mucositis, oral cavity fistulas, oral hemorrhage, and oral pain [6]. Among nervous system disorders, trigeminal nerve disorder is defined as a disorder characterized by involvement of the trigeminal nerve (fifth cranial nerve). However, the definition seems to imply diverse sensory dysfunction of the trigeminal nerve region and to overlap with peripheral neuropathy of the orofacial region. Trigeminal nerve disorders result in dulling of oral sensation, which decreases oral function. Although vincristine, which also shows neurotoxicity, is said to cause oral complications including trigeminal nerve disorders, trigeminal nerve disorders caused by other types of chemotherapeutic agents have not been well investigated [7].

The clinical use of taxanes has recently been increasing due to their strong chemotherapeutic effect, but reports of trigeminal nerve disorders are rare, though reports of peripheral neuropathy

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thy are increasing [5]. In this article, two patients with trigeminal nerve disorders, one involving the inferior alveolar nerve, the buccal nerve and the lingual nerve and the other the lingual nerve, due to docetaxel are described.

2. Case reports

2.1. Case 1

A 72-year-old man was referred to the oral surgery clinic for oral mucositis with numbness around the mouth. The patient had multiple cerebral metastases of lung adenocarcinoma (cT2aN0M1b (BRA), stage IV). At that point, the patient had received cranial irradiation (total dose of 30 Gy) and 4 courses of chemotherapy with carboplatin (AUC 6) plus pemetrexed (500 mg/m²) and bevacizumab (15 mg/m²) (CBDCA/PEM/BEV) and 11 courses of chemotherapy with pemetrexed (500 mg/m²) plus bevacizumab (15 mg/kg) (PEM/BEV). During these courses, there was no peripheral neuropathy or oral complications. However, as the size of the initial lung tumor increased, the patient started second-line chemotherapy with docetaxel (60 mg/m²) plus bevacizumab (15 mg/m²) (DTX/BEV). Five days after the start of DTX/BEV, numbness of the lower and upper extremities developed, and numbness of the skin around the mouth and tongue also appeared. On Day 7, although the numbness of the extremities was improved, the patient was referred to the oral surgery clinic for the oral mucositis. The oral examination showed severe mucositis with eating difficulty (grade 3 in CTCAE v4.0) (Fig. 1). Numbness of the right side of the tongue, buccal mucosa, and lower lip including the skin surface was found. The differential diagnosis of the numbness included central nervous system lesions and local lesions, such as the effects of oral mucositis, odontogenic infection, and primary or metastatic malignant tumor. Although the patient had metastatic brain tumors, numbness of the oral mucosa of cerebral origin was excluded based on the clinical appearance and the imaging diagnosis. Oral mucositis was also ruled out as a cause, because oral mucositis does not commonly cause numbness of the underlying peripheral nerve. Clinically, since the right second molar that was decayed with a radiolucent periapical area was asymptomatic, and the patient had not been taking a bisphosphonate drug, the possibility of odontogenic infection was low (Fig. 2). Since the patient's initial diagnosis was metastatic lung tumors, the possibility of mandibular metastatic tumor was considered. A Tc-scintigram showed slight accumulation at the mandible, but the accumulation was higher on the left side (Fig. 3). Magnetic resonance imaging showed no obvious bone destruction (Fig. 4). Thus, a malignant tumor, including primary tumor, was ruled out. The

oral diagnosis was trigeminal nerve disorders (grade 2), involving the inferior alveolar nerve, the buccal nerve and the lingual nerve with mucositis (grade 3). Since the symptoms were tolerable, the patient was followed up without treatment. On day 14, the numbness had improved slightly without medication, and on day 34 of follow-up, the numbness was diminished. Subsequently, the patient received three courses of chemotherapy with nivolumab (3 mg/kg) and two courses of reduced-dose docetaxel (50 mg/m²) (DTX). During this chemotherapy, peripheral neuropathy and oral numbness did not occur. The chemotherapy was then discontinued because the patient's physical strength decreased.

2.2. Case 2

A 67-year-old woman was referred to the oral surgery clinic for oral mucositis with a sensory disorder of the tongue. The patient had been continued on chemotherapy for serous adenocarcinoma of the ovary (cT3NxM0, stage III), which included one course of carboplatin (AUC 4.5) plus paclitaxel (150 mg/m²) (CBDCA/PTX) and two courses of carboplatin (AUC 5.0) plus paclitaxel (175 mg/m²) and bevacizumab (15 mg/kg) (CBDCA/PTX/BEV). Peripheral neuropathy with numbness of the upper and lower extremities occurred after the first course (grade 1), and it increased to grade 2 after the third course. The paclitaxel was then changed to docetaxel, and the fourth course of carboplatin (AUC 5.0) plus docetaxel (70 mg/m²) and bevacizumab (15 mg/kg) (CBDCA/DTX/BEV) was started. On day 4, a sensory disorder of the tongue newly appeared, and the peripheral neuropathy of the extremities had continued. On day 8, the patient was seen for oral mucositis, and, on examination, there was slight redness of the tongue without ulceration or tenderness (Fig. 5). Numbness of the right side of the tongue with dysgeusia was found, but there were no sensory disturbances of other parts of the oral cavity, including the skin surface around the mouth. Decreased tongue movement and drooping of the corners of the mouth suggesting facial nerve involvement were not present. Radiographically, there were no abnormal findings in the mandible (Fig. 6). The oral diagnosis was lingual nerve disorder (grade 1) with dysgeusia (grade 1) and slight mucositis (grade 1). Since the patient had already taken tramadol hydrochloride and pregabalin, and the symptoms were tolerable, no other medication was prescribed. The patient then continued the same regimen of four courses of chemotherapy. During the courses, the peripheral neuropathy of the extremities and the oral lingual nerve disorder continued. On day 170 of follow-up, the patient's tumor had stabilized, and the peripheral neuropathy and the lingual nerve disorder were completely resolved.



Fig. 1. Photograph of the oral examination. Oral mucositis with erythema and ulceration is found (A: Left side of the tongue, B: Buccal mucosa) (Case 1).

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